One size does not fit all-evolution of opioid agonist treatment in a naturalistic setting over 23 years

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Abstract: Background and aims Opioid agonist treatment (OAT) is currently the most effective treatment for people with opioid dependence. In most countries, however, access to the whole range of effective medications is restricted. This study aims to model the distribution of different OAT medications within a naturalistic and relatively unrestricted treatment setting (Zurich, Switzerland) over time, and to identify patient characteristics associated with each medication. Methods We used generalized estimating equation analysis with data from the OAT register of Zurich and the Swiss register for heroin-assisted treatment (HAT) to model and forecast the annual proportion of opioids applying exponential distributions until 2018 and patient characteristics between 1992 and 2015. Results Data from 11 895 patients were included in the analysis. Methadone remains the mainstay of OAT, being prescribed to two-thirds of patients. Following its approval, the proportion of HAT increased rapidly and is now constant at 12.16% [95% confidence interval (CI) = 11.15–13.17]. The initial increase of proportions of buprenorphine or slow-release oral morphine (SROM) following their approval for OAT was slower. While in 2014 both medications had a proportion of 10.2% and 10.3%, respectively, our model predicts a further increase of SROM to 19.9% in 2018, with a ceiling level of 25.19% (21.40–28.98%) thereafter. SROM patients display characteristics similar to those treated with methadone; buprenorphine patients show the highest social integration; and HAT patients are the most homogeneous group, with highest mean age, most widespread injecting experience and lowest social integration. Conclusions Based on data from Zurich, Switzerland from 1992 to 2015, there is no evidence for an excessive demand for a single medication in a naturalistic and liberal opioid agonist treatment setting. Rather, the specific patient characteristics associated with each medication underline the need for diversified treatment options for opioid dependence.

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One size does not fit all –evolution of opioid agonist treatments in a naturalistic setting over 23 years

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Abstract

Background and aims: Opioid agonist treatment (OAT) is currently the most effective treatment for people with opioid dependence. In most countries, however, access to the whole range of effective medications is restricted. This study aims to model the distribution of different OAT medications within a naturalistic and relatively unrestricted treatment setting (Zurich, Switzerland) over time, and to identify patient characteristics associated with each medication.

Methods: We used generalized estimating equation analysis with data from the OAT register of Zurich and the Swiss register for heroin-assisted treatment (HAT) to model and forecast the annual proportion of opioids applying exponential distributions until 2018 and patient characteristics between 1992 and 2015.

Results: Data from 11895 patients were included in the analysis. Methadone remains the mainstay of OAT, being prescribed to two thirds of patients. Following its approval, the proportion of HAT increased rapidly and is now constant at 12.2 % (95%CI 11.2-13.2). The initial increase of proportions of buprenorphine or slow-release oral morphine (SROM) following their approval for OAT was slower. While in 2015 both medications had a proportion of around 12% each, our model predicts a further increase of SROM to 19.9% in 2018, with a ceiling level of 25.2% (21.4 to 29.0%) thereafter. SROM patients display characteristics similar to those treated with methadone; buprenorphine patients show the highest social integration; and HAT patients are the most homogenous group, with highest mean age, most widespread injecting experience and lowest social integration.

Conclusions: Based on data from Zurich, Switzerland from 1992 to 2015, there is no evidence for an excessive demand for a single medication in a naturalistic and liberal opioid agonist treatment setting. Rather, the specific patient characteristics associated with each medication underline the need for diversified treatment options for opioid dependence.

Keywords: opioid; opiate; heroin; buprenorphine; methadone; morphine; register; opioid-assisted treatment

Background

Opioid dependence is a chronic disorder associated with negative consequences for affected individuals, their families and society [1-3]. Currently, North America is experiencing a severe opioid use epidemic which has recently been declared a "national emergency" [4, 5]. European surveillance data suggest a stable uptake of heroin but growing use of synthetic opioids and an increase of overdose-related deaths [6]. Opioid agonist treatment (OAT) is currently considered treatment of choice for opioid dependence [7]. For other psychiatric or medical disorders, such as major depression or hypertonia, patients and care providers can choose from various approved medications to identify the compound that is most effective and associated with the least side effects for each individual [8]. This is not the case for OAT, where often only methadone and/or buprenorphine are available due to regulatory constraints [9]. Other effective medications exist, but missing approval for OAT makes prescription extremely difficult in most settings. Moreover, patients who do not respond to conventional forms of OAT are usually denied heroin assisted treatment (HAT), a distinct and cost-effective variant of OAT that often leads to better outcomes [10]. HAT is only offered in select Western European countries and Vancouver [10-12]. Why is this so?

This conundrum may be partly explained by the stigma associated with illicit substance use, a lack of lobbying by an often marginalized group of patients or limited financial attractiveness for pharmaceutical companies (e.g. due to high regulatory demands, comparatively low costs of the market leader methadone, and lower price per dose ratios in OAT for substances already approved for pain treatment, e.g. hydromorphone). Diacetylmorphine (DAM, i.e. pharmaceutical heroin) is often a banned substance, and its manufacturing, import and use legally prohibited in many countries, factually rendering it impossible to prescribe. Stigmatization may contribute to the notion that opioid-dependent persons form a homogenous group that will equally benefit from the widely applied "one-size-fits-all" approach. Another important argument often put forth against the approval of diverse OAT forms is the concern of an increase in incidence and prevalence of opioid users; and of patients flocking to new treatments. The so-called "honey pot" effect postulates that large numbers of heroin users would enter HAT because of the "free" heroin [13], while other treatment options would be neglected and disappear [14]. However, the availability of a diversity of opioids for OAT is crucial to optimal treatment, e.g. buprenorphine or slow-release oral morphine sulfate (SROM)

should be available for patients with methadone-induced QTc-prolongation [15]. Therefore, scientists and clinicians have called for the expansion of pharmaceutical options in OAT [16].

However, empirical evidence on a larger scale about the distribution of different opioids used in OAT over time in a naturalistic setting with a diversity of substances available is lacking. Analysis of the Swiss treatment model can close this gap. Here, we use data from the OAT register of the canton of Zurich and the central Swiss HAT register to develop a comprehensive model that describes and forecasts the impact of the approval of additional opioid agonists for OAT on the prevalence of different medications over time. We also aimed to quantify the long-term effect of the admission stop to Swiss HAT from mid-1996 to March 1998, a consequence of the termination of the initial research phase and revision of relevant legislation [17]. Moreover, the characteristics (i.e. sex, lifetime injecting status, nationality, age, duration since first regular heroin use, and social integration) of subpopulations treated with different opioids are identified.

Methods

Databases

OAT register

Since 1991, the cantonal health authorities of Zurich mandate operation of an anonymized case register of OAT with methadone, buprenorphine and SROM. OAT providers are obliged to supply information at the beginning and end of each treatment episode, and every six months during ongoing treatment. Patients are identified unequivocally by an anonymized personal code.

HAT register

Since 1994, the Swiss Research Institute for Public Health and Addiction operates an anonymized case register of Swiss HAT. Providers must make information available at the beginning and end of treatment. All five institutions providing HAT in the canton of Zurich were asked to participate in this study and to provide an anonymized personal code as used in the OAT register. All but the smallest institution (with around 20 patients per year) provided data for the period between 1994 and 2015.

Statistical analysis

Calculations were based on the joint data of the OAT and HAT registers. As some patients received different opioids during a given year, we scored them in the following decreasing order: HAT=4, SROM=3, buprenorphine=2, and methadone=1. We utilized information from all available forms (entry, follow-up, cessation) using the maximum opioid score for each year in treatment. Thus, if a patient was in treatment at least one day of a year we computed one data point indicating the substance.

A slower or faster increase in the proportion of patients treated with a new substance after its approval can be described by an exponential distribution using a rate parameter α. When an additional parameter β is used to model the maximum level of a given substance in the data set, the annual proportion (G) of a new substance can be modelled as follows, with time as duration in years since introduction of the substance: $G=(1-\exp(-\alpha*time))*\beta/100$.

For example, if α is set at 0.3 and β is set at 20, a substance will reach a prevalence of 20% of all OAT after several years. In the first years after introduction of the substance, the increase in treatment proportion is largest and then becomes smaller (for this example 5.2% are treated with this substance in the first year, 9.0% in the second year, and 11.9% in the third year).

These modelings were done with heroin (since 1994), buprenorphine (since 2002), off-label SROM (from 2008 to 2012), and approved SROM (since 2013). Thus, we analyzed a multinomial distribution with up to five categories (i.e. five substances). Assuming that time span to establishment is similar for different substances, but distinct levels may be reached in the long term we tested models with a common α for all or for a certain group of substances.

Upon examination of our data, due to the HAT admission stop from mid-1996 to March 1998, we added an indicator γ to account for the restricted HAT access between 1997 and 2010. Thus, the proportion in treatment with the respective substance is modeled as $G=(1-\exp(-\alpha*time))*\beta/100*(1-\gamma/100)$, where time indicates year since introduction of the substance, α the rate parameter for increase, β the maximum level a substance will reach, and only for HAT γ the proportion of restricted access during 1997-2010. Notably, our model is based on the assumption that the increasing proportion of new opioids resulted in a decreasing proportion of patients with methadone only (i.e. other substances are not affected).

Although we are interested solely in the prevalence (proportion of patients) in OAT in a given year and thus apply a marginal model, we have to account for patients treated with the same substance for several years. We therefore applied a GEE2/ELS approach using PROC NLMIXED in SAS 9.4 similar to that proposed by Vonesh [18] (i.e. Program 4.17 for binary outcome). Our semi-parametric approach analyzes data by specifying "working" third- and fourth-order moments assuming normality (i.e. ELS) using an independence structure for the second-order moments of the repeated multinomial outcomes. Inference bases on a robust variance-covariance matrix of the model parameters via the EMPIRICAL option. Hereby the Gaussian-based negative log-likelihood is minimized (see appendix for details).

To test for differences between patient characteristics (sex, lifetime injecting status, nationality, age, duration since first regular heroin use (defined as using more than four times a week during a month) in years, and social integration index) by type of opioid we applied GEE2/ELS analyses (Program 4.17 in Vonesh [18]) on complete and imputed datasets (using the FCS algorithm in SAS 9.4 with 10 imputed datasets). The social integration index was computed as the mean of at least four of six items (having a full or part time job or run the household; earning one's living; living in a flat; having a partnership; good family relations; having friends outside the drug scene; Cronbach's Alpha = 0.58). Age was known for all 11985 patients, but there were missing data for sex (5.0%), social integration index (5.3%), lifetime injecting status (8.2%), nationality (13.8%), and duration since first regular opioid use (28.2%). To address not only marginal means but also probable increasing variance (i.e. for age, duration since first regular heroin use and social integration index) over the years 1992-2015 we aimed to specify appropriate but still parsimonious GEE2/ELS models (see appendix).

Collection and evaluation of data are in accordance with Swiss data protection laws, and the local ethics committee approved the analysis.

Results

We obtained 91836 data points indicating the opioid used from 11895 patients between 1992-2015. Mean annual number of patients in OAT in the canton of Zurich was 3826.5, with a minimum of 3056 in 1992 and a maximum of 4083 in 2008 (see appendix Table S1).

In 1992 and 1993 all patients were treated with methadone (Figure 1, bold lines). With the introduction of other opioids, the proportion of methadone treatments declined to 63.8% in 2015. Our statistical model fitted the observed data well (Table 1), as the dashed lines for fitted mean and the confidence interval region in Figure 1 reveal. The GEE2/ELS α-estimates in Table 1 indicate that the uptake of HAT (α=0.350; CI 95% 0.277-0.424) was faster than that of buprenorphine and SROM (α=0.259; CI 95% 0.212-0.305). The observed proportion of patients with buprenorphine, SROM and heroin, respectively, were similar in 2014 with 10 to 12%. However, the β-estimate indicating the maximum level is two to three times higher for SROM (β=25.19; CI 95% 21.40-28.98) than for buprenorphine (β=11.06; CI 95% 10.05-12.08) and heroin (β=12.16; CI 95% 11.15-13.17). As Figure 1 illustrates, the model forecasts that 19.85% (CI 95% 17.95-21.74) of OAT-patients in the canton of Zurich will be in SROM treatment in 2018.

-figure 1 here-

-table 1 here-

Our analysis also quantified the effect of the admission stop into HAT mandated from mid-1996 until 1998, which lasted 14 years (1997-2010). The proportion of patients excluded from HAT was substantial with an estimated 19.64% (CI 95% 15.01-24.26). Some patient characteristics, such as age and duration since first regular heroin use, changed substantially between 1992 and 2015. However, differences across opioids persisted (Figures 2 and 3). The main exception is sex, with an initial lower proportion of men in HAT due to oversampling of women in the PROVE study evaluating HAT [19].

-figures 2 and 3 here-

Over the whole study period the proportion of men (69.7% for methadone) was significantly higher for buprenorphine (+6.8%) and for SROM (+4.8%, see table S2 in appendix). While these differences are relatively small, the between-opioid differences with respect to injecting experiences are substantial: more than 80% in HAT, 63.3% with methadone, 54.7% with SROM, and 52.7% with buprenorphine had a history of injection use. A small declining time trend (-4.1% per decade) in the proportion of

patients with injecting experiences is found for HAT patients. The proportion of Swiss patients shows a small decline (-2.2% per decade) in all OATs, and is 6.5% higher in HAT than in methadone treatment.

The age of patients as well as the duration since first regular heroin use increased substantially between 1992 and 2015 (figure 3, table S3 in appendix). Patients in HAT are older than those on methadone, and those with buprenorphine or SROM are younger. Notably, the opposite applies for the variance among patient populations, with patients in HAT being the most homogenous and those in SROM treatment the least homogenous group. For example, the variance of the duration since first regular heroin use is estimated at 85.2 for those patients with SROM and 51.7 for those with heroin in 2015, i.e. 65% higher for SROM than for heroin.

According to the social integration index (varying between 0 and 10 with higher values indicating better social integration), patients on buprenorphine had a mean value of 6.5 and were thus better integrated than those on methadone (5.9), SROM (5.9), or those in HAT who were least integrated (5.1). Taking the variance (=6.4) into account, the effect sizes between methadone and buprenorphine (Cohen's d=0.23) and heroin (d=0.32) respectively could be classified as weak, and between buprenorphine and heroin (d=0.55) as moderate. Notably, the model estimated a time effect only for the variance model and not for the mean model, indicating that social integration has become more diverse over calendar years.

Discussion

Our analysis of register data over more than two decades illustrates how newly approved opioids for OAT are adopted by the treatment system when a wider selection is available. After approval and an initial increase, the proportion of treatments with a newly approved opioid stabilizes in a predictable manner. By showing substantial demand for each of the approved medications, our findings suggest a need for diversity of opioid agonists to be available for OAT. We also identified differing patient characteristics for specific opioids, indicating that the prescription of opioids for OAT is not a random process. Differences between HAT and conventional OAT persisted over time, illustrating that the target population of severely dependent individuals is indeed receiving this therapy. Our results also indicate the large impact of regulatory framework and political decisions to limit or approve treatments as illustrated by the

consequences of temporary restricted access to HAT, or the introduction of buprenorphine or SROM treatments.

Importantly, the approval of new opioids for OAT did not attract large numbers of patients to these treatments. While the choice of methadone in Zurich has been continuously diminishing with the approval of other opioids for OAT, it was still used in almost two thirds of treatments in 2015. The available alternative opioids, i.e. DAM, buprenorphine and SROM, have a proportion of around 10% each. However, our model forecasts that, while the use of DAM (approved in 1994) and buprenorphine (approved in 2002) has already reached its ceiling, the use of SROM (approved in 2013) will increase during the next few years to a level two to three times higher. This increase is plausible, as SROM is associated with less adverse effects than methadone [15] with similar retention in treatment [20]. It may therefore be more appropriate for younger patients entering OAT for the first time as well as for an overall aging OAT population[21] more prone to adverse effects such as QTc-prolongation[22]. The recent approval of levomethadone in Switzerland in 2015 may contribute to a further reduction of the proportion of OATs with conventional methadone in the future.

Buprenorphine, like SROM, is associated with fewer adverse effects than methadone, but the complicated induction procedure due to its properties as a partial agonist may limit its use and contribute to the slightly lower retention in treatment compared to methadone particularly during the first weeks of treatment [23]. However, newer, more convenient induction methods may lead to an expansion of buprenorphine use [24]. The comparatively small proportion of patients on buprenorphine contrasts with, for instance, France or North America, where there is a movement supporting buprenorphine over methadone. This is likely a consequence of the superior safety profile of buprenorphine concerning respiratory depression, as well as the regulatory framework in these settings, permitting only the prescription of buprenorphine in office-based settings. Moreover, in North America buprenorphine is most frequently prescribed in combination with naloxone to putatively reduce diversion and misuse. This combination was approved in Switzerland only recently in 2017. Importantly, there is no regulatory difference in Switzerland between the provision of OAT with methadone, SROM or buprenorphine regarding office-based or institutional settings, take-home dosages or supervised intake. Furthermore, because of low overdose numbers and the ongoing decline of incidence of opioid use in Switzerland [25], the

concerns about diversion of opioid agonists and the incentive to prescribe the partial agonist buprenorphine may be less pronounced. Our data also suggest that in a patient-centered regulatory framework offering several alternative opioid medications, patients often prefer a full agonist over buprenorphine.

Concerns about newly approved treatments attracting large numbers of patients entering OAT ("honey pot" effect [13]) are unwarranted. While the demand for HAT after initial approval was indeed faster than that of buprenorphine or SROM, the proportion of HAT treatments has remained stable even after the removal of the admission restriction in March 1998, with treatment capacities exceeding demand [26]. The rather restrictive HAT setting, requiring personal visits to the treatment center two to three times daily for dispensing and application of the substance, may have limited its attractiveness. Many patients who would qualify for HAT decline to enter for this reason [27]. Nevertheless, the impact of the 1996-1998 moratorium lasted until 2010, indicating that around one fifth of patients were precluded from entering HAT.

Across all opioids, the population of opioid-dependent patients in Switzerland is an aging cohort [21], which can be linked to a declining incidence of opioid use and high long-term treatment participation [25, 28]. Throughout the study period, age and duration since first regular heroin use increased substantially (Figure 3).

Our study identifies distinctive characteristics of populations receiving different opioids. Assuming that patients and providers are likely to choose the most favorable opioid for treatment, subpopulations benefitting from a specific medication should become evident over time. From both the patient and provider perspective, this underlines the need for the expansion of treatment options [16]. Compared to methadone patients, SROM and buprenorphine patients are slightly younger and accordingly have a somewhat shorter duration since first regular heroin use. They are also more likely to be men and have less injecting experience. The routes of administration in opioid-dependent persons have changed during the past decades in Europe, with smoking and snorting becoming more popular [6]. Importantly, patients on buprenorphine show better social integration compared to patients on all other opioids.

The HAT population is the most homogenous subgroup, although we did not differentiate between patients treated with injectable or oral DAM. Compared to those on methadone, HAT patients have a somewhat higher mean age and longer duration since first regular heroin use, are more likely to be Swiss, and have injecting experience.

Social integration is significantly lower than for the other opioids, in particular compared to patients on buprenorphine. These characteristics can be linked to the clear-cut inclusion criteria for this form of OAT, designed to select severely dependent individuals: Patients must be at least 18 years old, have a history of severe opioid dependence of more than two years, must have failed at least two conventional treatments and have documented social or health problems related to opioid dependence.

Limitations and Strengths

Several limitations need to be considered when interpreting our data. We have no data on OAT outside of Zurich, so we cannot rule out that some patients obtained treatment with other opioids before, in-between or after OAT-episodes in Zurich. When patients were prescribed several opioids in a given year, we ranked the different substances in order to categorize them. This may have led to a slight underestimation of buprenorphine, SROM and methadone treatments. Furthermore, as substance use is influenced by local trends, our data may not be generalizable to all settings offering low-threshold OAT with different opioids.

DAM is approved for HAT in oral as well as injectable form. However, no data on route of administration were available precluding further differentiation. It is possible that patients on injectable DAM would show differing characteristics from those treated only with the oral form.

It has to be pointed out, that, although it has been associated with reduction in risk of all cause and overdose mortality [29], retention can only be a proxy measure of outcome. The fact that a group of patients is in treatment with a substance does not imply that this treatment is the most effective for this group, e.g. the fact that patients on buprenorphine show highest social integration does not imply that socially well integrated patients should receive buprenorphine.

Among the strengths of our study are the large sample size, the use of data from different registers including HAT, and the length of the observation period. Switzerland is among the few countries where a variety of opioids is available for OAT, and prescription depends largely on patients and providers rather than regulatory constraints.

Conclusions

Modelling of register data from Zurich, Switzerland, allows describing past and current distributions of different medications used in OAT, identifying associated patient characteristics and predicting future distributions of opioid medications in OAT. There is no evidence for an excessive demand for a single opioid following its approval or for an increase of the overall number of OAT patients over time. The subpopulations treated with different opioids display specific characteristics, with SROM-patients being most like those on methadone, buprenorphine patients showing the best social integration, and HAT-patients being the most homogenous group, with the highest mean age, most injecting experience and lowest social integration.

For other chronic diseases such as diabetes or hypertension, it is widely accepted that a diversified range of medications boosts the likelihood of providing the optimal (i.e. the most effective and best tolerated) treatment for each individual. In OAT this selection is often limited due to regulatory restrictions. The study findings indicate that there is a need for a diversity of opioid agonists available for OAT to identify the optimal treatment option for each individual with opioid dependence.

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Ethical principles

The authors certify that

- the material has not been published in whole or in part elsewhere;
- the paper is not currently being considered for publication elsewhere;

- all authors have been personally and actively involved in substantive work leading to the report, and will hold themselves jointly and individually responsible for its content;
- all relevant ethical safeguards have been met in relation to patient or subject protection.

References

1. Degenhardt L., Bucello C., Mathers B., Briegleb C., Ali H., Hickman M. *et al.* Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction* 2011; **106**: 32-51.
2. Hser Y. I., Evans E., Grella C., Ling W., Anglin D. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015; **23**: 76-89.
3. McLellan A. T., Lewis D. C., O'Brien C. P., Kleber H. D. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000; **284**: 1689-95.
4. McCarthy M. US declares opioid epidemic a "national emergency". *BMJ* 2017; **358**: j3881.
5. Rudd R. A., Aleshire N., Zibbell J. E., Gladden R. M. Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. *MMWR Morb Mortal Wkly Rep* 2016; **64**: 1378-82.
6. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2017: Trends and Developments*. Luxembourg: Publications Office of the European Union; 2017. Available at: http://www.emcdda.europa.eu/publications/edr/trends-developments/2017 (accessed June 7th, 2017).
7. World Health Organization *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence.* Geneva: World Health Organization; 2009.
8. Rush A. J., Trivedi M. H., Wisniewski S. R., Nierenberg A. A., Stewart J. W., Warden D. *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; **163**: 1905-17.
9. European Monitoring Centre for Drugs and Drug Addiction. *Data and statistics: Opioid substitution treatment clients by OST medication* 2017. Available at: http://www.emcdda.europa.eu/data/stats2017/hsr (accessed June 19th).
10. Strang J., Groshkova T., Uchtenhagen A., van den Brink W., Haasen C., Schechter M. T. *et al.* Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *Br J Psychiatry* 2015; **207**: 5-14.
11. Nosyk B., Guh D. P., Bansback N. J., Oviedo-Joekes E., Brissette S., Marsh D. C. *et al.* Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ* 2012; **184**: E317-28.
12. Farrell M., Hall W. Heroin-assisted treatment: has a controversial treatment come of age? *Br J Psychiatry* 2015; **207**: 3-4.
13. Bammer G., Dobler-Mikola A., Fleming P. M., Strang J., Uchtenhagen A. The heroin prescribing debate: integrating science and politics. *Science* 1999; **284**: 1277-8.
14. Uchtenhagen A. Heroin-assisted treatment in Switzerland: a case study in policy change. *Addiction* 2010; **105**: 29-37.
15. Hammig R., Kohler W., Bonorden-Kleij K., Weber B., Lebentrau K., Berthel T. *et al.* Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat* 2014; **47**: 275-81.
16. Nosyk B., Anglin M. D., Brissette S., Kerr T., Marsh D. C., Schackman B. R. *et al.* A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff (Millwood)* 2013; **32**: 1462-9.
17. Gschwend P., Rehm J., Lezzi S., Blattler R., Steffen T., Gutzwiller F. *et al.* Development of a monitoring system for heroin-assisted substitution treatment in Switzerland. *Soz Praventivmed* 2002; **47**: 33-8.
18. Vonesh E. *Generalized Linear and Nonlinear Models for Correlated Data : Theory and Applications Using SAS.* Cary: SAS Institute; 2012.
19. Uchtenhagen A., Gutzwiller F., Dobler-Mikola A. *Versuche für eine ärztliche Verschreibung von Betäubungsmitteln: Abschlussbericht der Forschungsbeauftragten: Synthesebericht [Programme for a medical prescription of narcotics: final report of the research representatives. Synthesis report.]*. Zürich, Switzerland: Institute for Social and Preventive Medicine University of Zürich; 1997. Available.

20. Beck T., Haasen C., Verthein U., Walcher S., Schuler C., Backmund M. *et al.* Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction* 2014; **109**: 617-26.
21. Dursteler-MacFarland K. M., Vogel M., Wiesbeck G. A., Petitjean S. A. There is no age limit for methadone: a retrospective cohort study. *Subst Abuse Treat Prev Policy* 2011; **6**: 9.
22. Bart G., Wyman Z., Wang Q., Hodges J. S., Karim R., Bart B. A. Methadone and the QTc Interval: Paucity of Clinically Significant Factors in a Retrospective Cohort. *J Addict Med* 2017; **11**: 489-493.
23. Mattick R. P., Breen C., Kimber J., Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014: CD002207.
24. Hammig R., Kemter A., Strasser J., von Bardeleben U., Gugger B., Walter M. *et al.* Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil* 2016; **7**: 99-105.
25. Nordt C., Landolt K., Stohler R. Estimating incidence trends in regular heroin use in 26 regions of Switzerland using methadone treatment data. *Subst Abuse Treat Prev Policy* 2009; **4**: 14.
26. Hiltebrand D., Dey M., Mayorova E., Bolliger H., Schaub M. P. *Heroin-assisted treatment in Switzerland - Results of 2015 survey*. Zürich; 2016. Available at: https://www.bag.admin.ch/dam/bag/en/dokumente/npp/drogen/sucht/heroingestuetzte-behandlung-resultate-2015-deutsch.pdf.download.pdf/HeGeBe_Jahresbericht_2015_EN.pdf.
27. Schmid O., Müller T., Wiesbeck G. A., Dürsteler-MacFarland K. M. Felderhebung im Schweizer Drogenmilieu 2008 [Field study in the Swiss drug scene 2008]. *Abhängigkeiten* 2009; **15**: 40-47.
28. Nordt C., Vogel M., Dursteler K. M., Stohler R., Herdener M. A comprehensive model of treatment participation in chronic disease allowed prediction of opioid substitution treatment participation in Zurich, 1992-2012. *J Clin Epidemiol* 2015; **68**: 1346-54.
29. Sordo L., Barrio G., Bravo M. J., Indave B. I., Degenhardt L., Wiessing L. *et al.* Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357**: j1550.

Table 1: GEE2/ELS estimates modeling the proportion of substances in opioid agonist treatment, canton of Zurich 1992-2015.

				CI 95%	
	Estimate	SE	p	Lower	Upper
α Buprenorphine/SROM	0.259	0.024	<.0001	0.212	0.305
α Heroin	0.350	0.037	<.0001	0.277	0.424
β Buprenorphine	11.06	0.518	<.0001	10.05	12.08
β SROM	25.19	0.193	<.0001	21.40	28.98
β Off-label SROM	2.529	0.280	<.0001	1.981	3.078
β Heroin	12.16	0.515	<.0001	11.15	13.17
γ Heroin	19.64	2.359	<.0001	15.01	24.26
Number of patients	11895				
Number of observations	91836				
-2 Log-Likelihood	92816				

Notes: Proportion in treatment $G_{Substance} = (1-\exp(-\alpha_{Substance}*time))*\beta_{Substance}/100*(1-\gamma_{Heroin}/100)$; time = time in years since introduction of substance; α = rate parameter of substance in years; β = maximum level of substance in percent; γ = Proportion restricted access during 1997-2010 for heroin in percent; SE = standard error, CI = confidence interval, SROM = slow release oral morphine sulfate. Proportion of methadone (1992-2015) is 1 minus $G_{Heroin\ (1994-2015)} - G_{Buprenorphine\ (2002-2015)} - G_{Off-label\ SROM\ (2008-2012)} - G_{SROM\ (2013-2015)}$.

Figure 1: Proportion of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015.

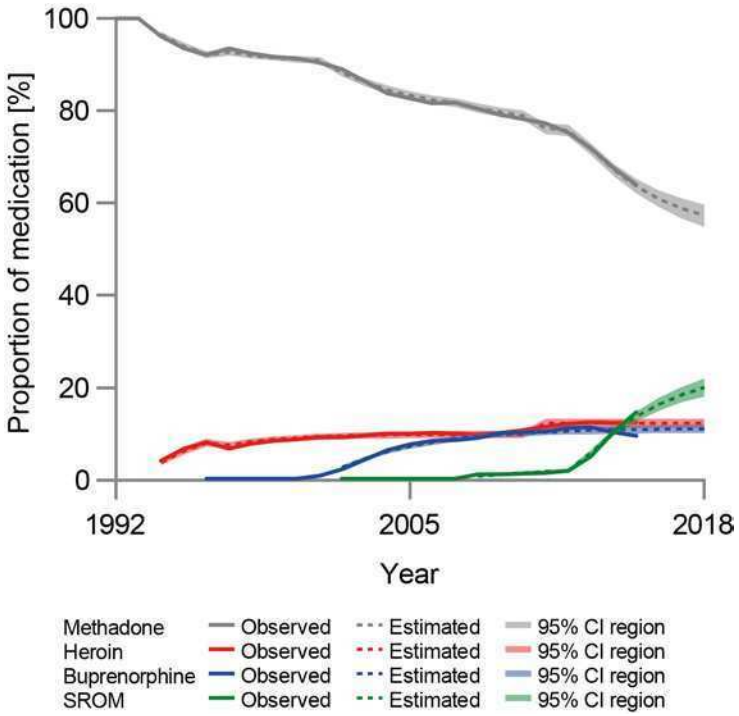


Figure 2: Sex, lifetime injecting status and nationality of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015

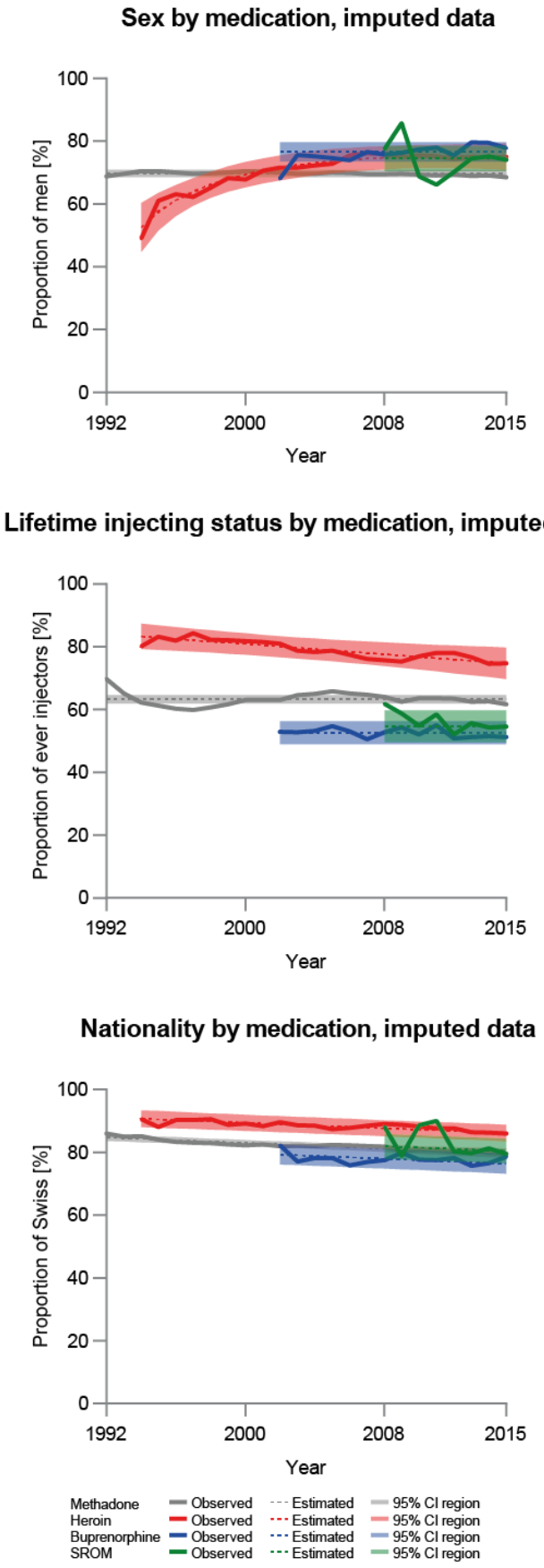
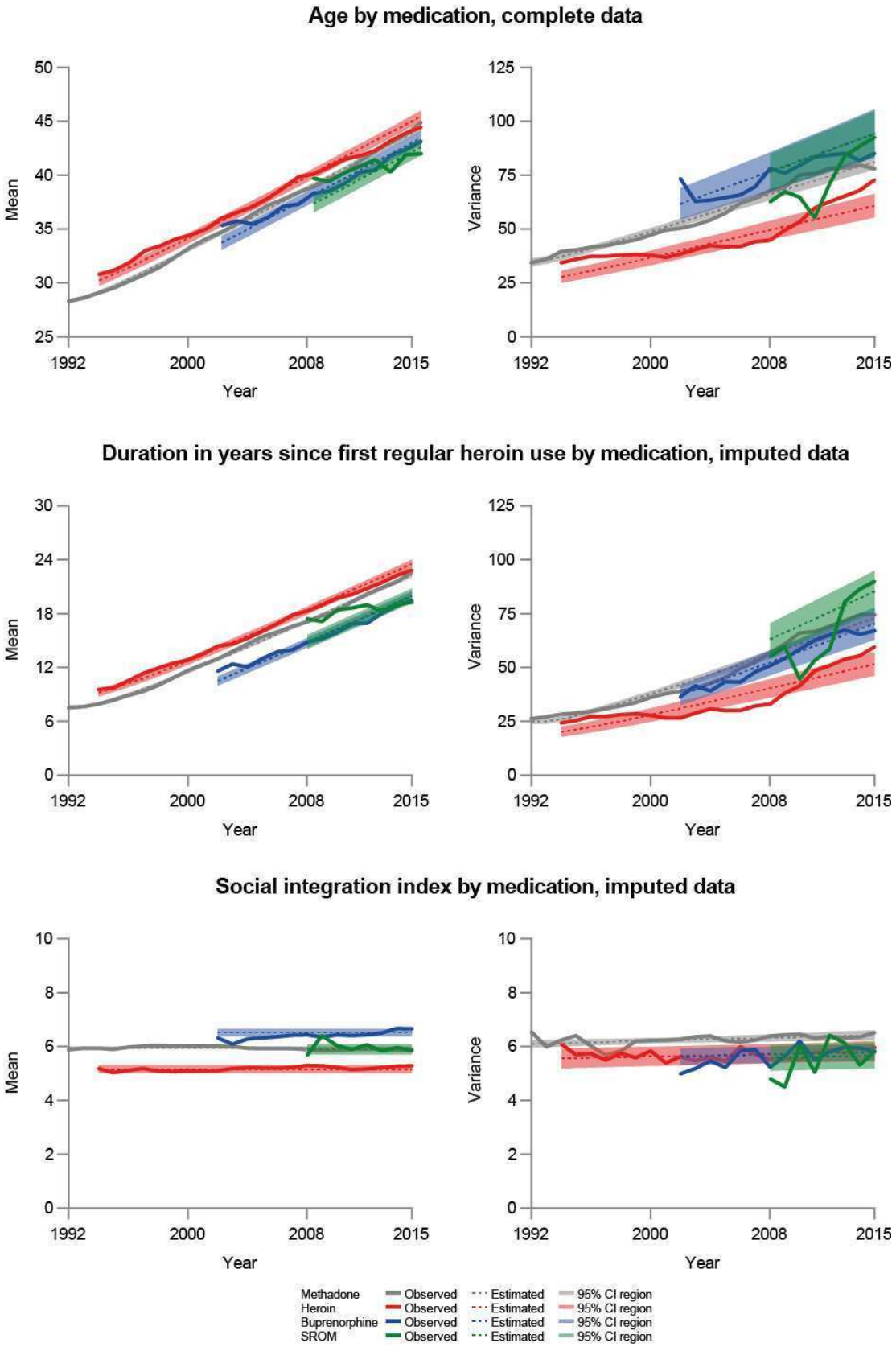


Figure 3: Mean and variance of age, duration since first regular heroin use in years and social integration index of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015



Appendix

One size does not fit all –evolution of opioidagonist treatments in a naturalistic setting over 23 years

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OAT-Regulatory Framework in Zurich, Switzerland.

Until 2015, four different opioids were approved for OAT in Switzerland. In July 2015, levomethadone was approved for OAT, but could not be considered in this analysis yet. Methadone treatment for select patients started in 1975. Since 1992, low-threshold treatment programs (opioid dependence as only prerequisite, covered by health insurance, no abstinence requirements, few differences between office-based and institutional provision) were introduced and a sizable number of opioid-dependent patients entered OAT. In 1994, HAT was initiated in the canton of Zurich. Patients are only eligible for HAT if they are at least 18 years old, have a history of severe opioid dependence of more than two years, have failed at least two conventional treatments (for instance, OAT with another opioid or detoxification) and have documented social and/or health problems related to opioid dependence. From mid-1996 to March 1998 no new patients were admitted to HAT for legal reasons [1]. In 2002, buprenorphine was introduced. Until 2012, only a few patients were treated with different kinds of off-label SROM, but in 2013 an SROM formulation has been approved for OAT. Mandatory health insurance covers the costs of OAT with every approved substance. After special instruction in addiction medicine any physician may provide OAT. At least since 1992 there are sufficient treatment slots for all opioid-dependent patients who desire to enter OAT. However, as the prescription of diacetylmorphine (i.e. pharmaceutical heroin) is strictly controlled in Switzerland, only specialized institutions provide HAT and the number of treatment slots is regulated by the Swiss Federal Office of Public Health. In 2015, around 10% of approved treatment slots in Switzerland were unoccupied [2]. Diacetylmorphine is the only substance approved for injectable OAT.

Statistical analysis - extended information

Sex was known for 11303 of the 11895 patients, nationality was known of 10258 patients and lifetime injecting status was known of 10914 patients. 5581 patients had injected heroin at least once before their first registration in the OAT register, 1476 patients (13.5%) had injected at least once in their lifetime after first registration in OAT, and 3857 patients (35.3%) had never injected heroin. Specifically, if a change in lifetime injection status could be observed in the OAT register data depends among others on the observation duration in the register ("OAT-time" = last minus first year in OAT). Therefore, for those who changed lifetime injection status we computed a variable

“pinjectchange” = (year of lifetime injecting change - year of first OAT)/OAT-time, a variable ranging between 0 and 1.). The forth variable requiring imputation in the first stage was year of first regular heroin use, which was also checked for plausibility as follows. For 3352 (28.2%) of the 11895 patients, we could not obtain a plausible year of first regular heroin use (not before their 12th year of age, not after their first OAT [according to our case register], difference in cases of multiple entry forms 3 years or less). Similar to “pinjectchange” a variable “ponsety” = (year of first regular heroin use – year of birth – 11)/(year of first OAT – year of birth – 11), a variable ranging between 0 and 1 was computed for imputation in order to obtain values within plausible limits. At least one social integration index value was known for 11261 patients of the 11895 patients. In contrast with sex, lifetime injecting status and nationality we assumed that the social integration index may vary from year to year. From the OAT register we could compute for 75883 annual data points a social integration index value of the 91836 data points. Since our case register is far from being a balanced repeated-measure dataset—where all patients provide the same number of follow-up datasets within the similar time period—we applied a two-stage approach for multiple imputation. The first stage included invariant personal characteristics in which we used the mean value of all variables of our model of interest, with fully conditional specification variables (ie, year of first OAT, “OAT-time”, sex, social integration index, “pinjectchange”, lifetime injecting status, nationality, and “ponsety”). After imputation for those imputed as beginning injection after first OAT the year of change were calculated as follows: year of lifetime injecting change = ceil(“pinjectchange”*”OAT-time” + year of first OAT). The onset year was computed accordingly as: year of first regular heroin use = ceil(“ponsety”* (year of first OAT – year of birth – 11) + year of birth + 11), In 0.05 percent this lead to a improbable onset year before 1965 or earlier; in few these cases a corrected year of onset was computed as the midpoint of the initially imputed onset year and the year of first OAT. The second-stage imputation used difference variables (indicating the difference of an observed value to the person’s specific mean value from the first stages) for the social integration index, the year of treatment and all variables of the first stage imputation. Finally, those imputed values of the social integration index that lay outside the range of 0 to 10 (less than 1 %) were set to the respective limit value.

References

1. Gschwend P., Rehm J., Lezzi S., Blattler R., Steffen T., Gutzwiller F. *et al.* Development of a monitoring system for heroin-assisted substitution treatment in Switzerland. *Soz Praventivmed* 2002; **47**: 33-8.
2. Hiltebrand D., Dey M., Mayorova E., Bolliger H., Schaub M. P. *Heroin-assisted treatment in Switzerland - Results of 2015 survey*. Zürich; 2016. Available at: https://www.bag.admin.ch/dam/bag/en/dokumente/npp/drogen/sucht/heroingestuetzte-behandlung-resultate-2015-deutsch.pdf.download.pdf/HeGeBe_Jahresbericht_2015_EN.pdf.

Table S1: Number of patients by opioid-assisted treatment form, 1992-2015 canton of Zurich

Year	Methadone	Diacetylmorphine	Buprenorphine	SROM	Total
1992	3056	0	0	0	3056
1993	3376	0	0	0	3376
1994	3489	146	0	0	3635
1995	3615	252	0	0	3867
1996	3399	296	1	0	3696
1997	3573	252	0	0	3825
1998	3688	305	0	0	3993
1999	3622	331	1	0	3954
2000	3616	344	5	0	3965
2001	3573	358	27	0	3958
2002	3612	367	84	1	4064
2003	3492	381	170	4	4047
2004	3406	399	258	5	4068
2005	3316	394	300	6	4016
2006	3279	402	334	6	4021
2007	3298	397	342	5	4042
2008	3279	397	367	40	4083
2009	3200	402	406	42	4050
2010	3102	420	406	47	3975
2011	2936	429	390	51	3806
2012	2754	439	405	68	3666
2013	2580	442	404	174	3600
2014	2404	433	365	368	3570
2015	2235	434	326	508	3503

SAS syntax to estimate the multinomial distribution of substance between 1992 and 2015 accounting for repeated measurement

```
proc nlmixed  empirical data=file ;

parm  a2=.25 a1=.3 b2=10 b3=3  b4=30 b1=11 c1=20 ;

 a4=a2;

a3=a2;

lik1 = (1-exp(-a1*(year-1994+1)))*b1/100*(year>1993)*(1-
c1*(1997<=year<=2010)/100);

lik2 = .000001+(1-exp(-a2*(year-2002+1)))*b2/100*(year>=2002);

lik3 = .000001+(1-exp(-a3*(year-2008+1)))*b3/100*(2008<=year<=2012)+(1-exp(-
a4*(year-2013+1)))*b4/100*(year>=2013);

IF opioidy = 4 Then lik = lik1+u;

Else IF opioidy = 2 Then lik = lik2+u;

Else IF opioidy = 3 Then lik = Lik3+u;

Else lik = 1-lik1-lik2-lik3+u;

ll = log(lik);

model opioidy ~ general(ll);

random u ~ normal(0,0) subject=id;

run;
```

“empirical”: requests the likelihood-based empirical estimator of the covariance matrix

“file”: the name of the dataset with variables as described below

“parms …”: specify parameter names and initial values

“a4=a2”, “a3=a2” estimate a joint α parameter for buprenorphine, off-label SROM and approved SROM as identical to α of

“year”: calendar year

“lik1”: fitted proportion of patients with heroin

“a1”: α rate parameter for the exponential increase of heroin

“b1”: β maximum proportion of patients with heroin in percent

“c1”: γ proportion of restricted access to heroin 1997-2010 in percent

“lik2”: fitted proportion of patients with buprenorphine

“a2”: α rate parameter for the exponential increase of buprenorphine

“b2”: β maximum proportion of patients with buprenorphine in percent

“.000001+” a (very small) proportion needed to allow the rare observations of buprenorhine before 2002

“lik3”: fitted proportion of patients with off-level SROM

“a3”: α rate parameter for the exponential increase of off-level SROM

“b3”: β maximum proportion of patients with off-level SROM in percent

“.000001+” a (very small) proportion needed to allow the rare observations of off-level SROM before 2008

“lik4”: fitted proportion of patients with approved SROM

“a4”: α rate parameter for the exponential increase of approved SROM

“b4”: β maximum proportion of patients with approved SROM in percent

“opioidy”: the observed substance of the patient in the respective year (methadone=1, buprenorphine=2, SROM=3, heroin=4)

“Else lik = 1-lik1-lik2-lik3” computes the proportion of patients with methadone as 1 minus the other three proportions

“ll = log(lik)” specifies the multinomial log-likelihood directly using ‘general(ll)’

“id”: patient identification

“u”: patient specific effect with mean and variance set to 0

Table S2: GEE2/ELS estimates modelling sex, lifetime injecting status and nationality of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015

		Complete dataset			Imputed dataset		
Proportion of men		Estimate	SE	P	Estimate	SE	P
	Intercept (ref: methadone)	0.696	0.006	<.0001	0.697	0.006	<.0001
	Buprenorphine	0.069	0.016	<.0001	0.068	0.016	<.0001
	SROM	0.049	0.020	0.0155	0.048	0.020	0.0188
	Heroin	-0.383	0.084	<.0001	-0.373	0.085	<.0001
	Heroin * time	-0.099	0.044	0.0251	-0.094	0.045	0.0350
	Heroin * logtime	0.209	0.054	0.0001	0.203	0.055	0.0002
	Number of patients	11303			11895		
	Number of observations	89340			91836		
	-2 Log-Likelihood	108589			111624		
Proportion of ever injectors		Estimate	SE	P	Estimate	SE	P

	Intercept (ref: methadone)	0.637	0.006	<.0001	0.633	0.007	<.0001
	Buprenorphine	-0.106	0.019	<.0001	-0.106	0.019	<.0001
	SROM	-0.073	0.023	0.0020	-0.086	0.024	0.0005
	Heroin	0.220	0.022	<.0001	0.208	0.023	<.0001
	Heroin * time	-0.046	0.015	0.0022	-0.041	0.015	0.0054
	Number of patients	10914			11895		
	Number of observations	88383			91836		
	-2 Log-Likelihood	114104			118929		
Proportion of Swiss		Estimate	SE	P	Estimate	SE	P
	Intercept (ref: methadone)	0.847	0.006	<.0001	0.847	0.006	<.0001
	Time	-0.022	0.004	<.0001	-0.022	0.004	<.0001
	Buprenorphine	-0.032	0.016	0.0607	-0.032	0.016	0.0437
	SROM	0.007	0.020	0.6744	0.007	0.020	0.7287
	Heroin	0.065	0.013	<.0001	0.065	0.013	<.0001
	Number of patients	10258			11895		

Number of observations	82188	91836
-2 Log-Likelihood	75396	84588

Notes: time = (year-1992)/10; logtime = ln(year-1991); SE = standard error, SROM = slow release oral morphine sulfate

Table S3: GEE2/ELS estimates modelling mean and variance of age, duration since first regular heroin use in years and social integration index of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015

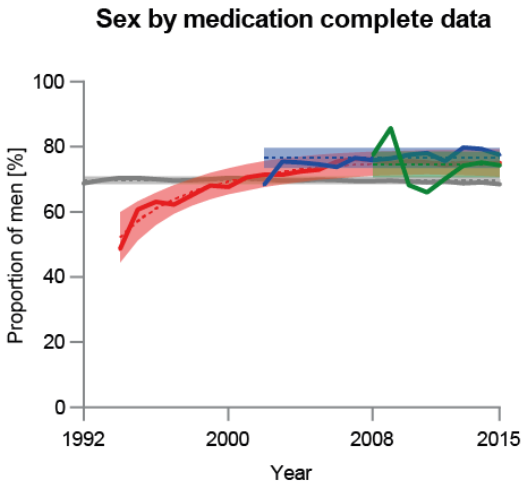
			Complete dataset			Imputed dataset
Age			Estimate	SE	P	
	Mean model (Mm)	Intercept (ref: methadone)	28.25	0.11	<.0001	not needed as age is known for all patients
		Time	7.86	0.14	<.0001	
		Logtime	-0.62	0.09	<.0001	
		Buprenorphine	-0.92	0.34	0.0061	
		SROM	-1.75	0.41	<.0001	
		Heroin	1.08	0.25	<.0001	
	Variance model (Vm age)	Varunit (ref: methadone)	2.89	0.13	<.0001	
		Varadd Buprenorphine	0.16	0.07	0.0243	
		Varadd SROM	0.16	0.07	0.0172	
		Varadd Heroin	-0.25	0.04	<.0001	
		Minval	16.26	0.72	<.0001	
		Number of patients	11895			

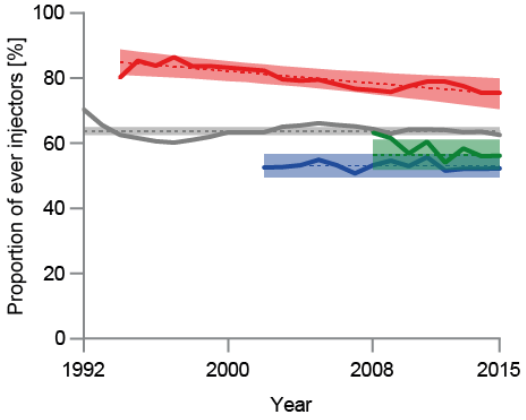
	Number of observations	91836					
	-2 Log-Likelihood	627371					
Duration since first regular heroin use		Estimate	SE	P	Estimate	SE	P
Mean model (Mm)	Intercept (ref: methadone)	7.82	0.12	<.0001	7.64	0.10	<.0001
	Time	7.98	0.15	<.0001	7.92	0.13	<.0001
	Logtime	-1.33	0.10	<.0001	-1.11	0.08	<.0001
	Buprenorphine	-2.77	0.30	<.0001	-2.40	0.28	<.0001
	SROM	-2.22	0.51	<.0001	-2.32	0.40	<.0001
	Heroin	1.09	0.23	<.0001	1.20	0.22	<.0001
Variance model (Vm duration)	Varunit (ref: methadone)	3.46	0.06	<.0001	3.27	0.05	<.0001
	Varadd Buprenorphine	-0.01	0.06	0.9239	0.08	0.06	0.1796
	Varadd SROM	0.34	0.09	0.0001	0.31	0.07	<.0001
	Varadd Heroin	-0.38	0.03	<.0001	-0.33	0.04	<.0001
	Number of patients	8543			11895		
	Number of observations	64688			91836		

	-2 Log-Likelihood	427885			605660		
Social integration index		Estimate	SE	P	Estimate	SE	P
Mean model (Mm)	Intercept (ref: methadone)	5.96	0.03	<.0001	5.95	0.02	<.0001
	Buprenorphine	0.59	0.08	<.0001	0.56	0.07	<.0001
	SROM	-0.06	0.10	0.5205	-0.06	0.10	0.559
	Heroin	-1.21	0.08	<.0001	-0.80	0.08	<.0001
Variance model (Vm social)	Varunit (ref: methadone)	6.41	0.11	<.0001	6.43	0.11	<.0001
	Vartime	-0.01	0.07	0.1495	-0.14	0.06	0.0232
	Varadd Buprenorphine	-0.09	0.03	0.0006	-0.10	0.03	0.0002
	Varadd SROM	-0.11	0.04	0.0130	-0.12	0.04	0.0038
	Varadd Heroin	-0.11	0.03	0.0011	-0.09	0.03	0.0018
	Number of patients	11182			11895		
	Number of observations	75883			91836		
	-2 Log-Likelihood	354232			427600		

Notes: time = (year-1992)/10; logtime = ln(year-1991); Vartime = 2016-year; Mm = Mean model; VM age = Variance model for age = (Varunit+Vartime)*(1+$Varadd_{Medication}$)*(Mm-Minval), i.e. the last term (Mm-Minval) indicate that the variance increase linearly with increasing mean age of patients – 16.26 years over the observation period; VM duration = Variance model for duration since first regular heroin use in years = (Varunit+Vartime)*(1+Varadd)*(Mm), i.e. the last term (Mm) indicate that the variance increases linearly with the mean duration since first regular heroin use of patients over the observation period; VM social = Variance model for social integration index = (Varunit+Vartime)*(1+Varadd).

Figure S1 Sex, lifetime injecting status and nationality of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015





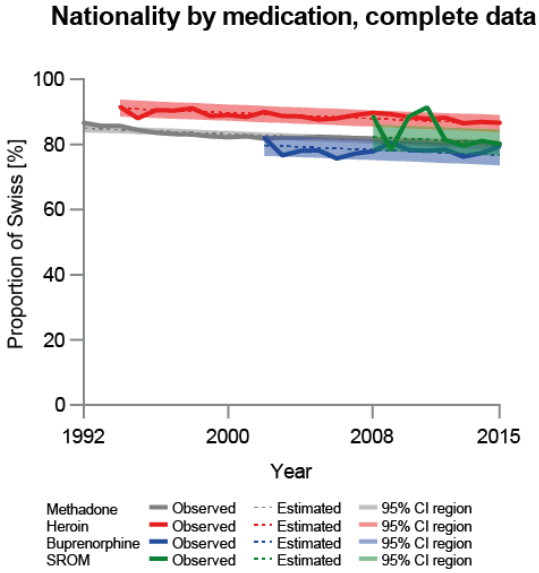


Figure S2 Mean and variance of age, duration since first regular heroin use in years and social integration index of patients in opioid agonist treatment by medication, canton of Zurich 1992-2015